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A Fatal Case Involving Proparacaine

Proparacaine, also known as proxymetacaine, 2-diethylaminoethyl 3-amino-4-propoxybenzoate hydrochloride, is a topical anesthetic used in ophthalmology. It is sold under various trade names in a 0.5% aqueous solution.

This case involved the inhalation of the drug in powder form in much the same manner as cocaine is ordinarily introduced into the system by drug abusers. A search of the literature failed to reveal any other fatal cases.

Case History

A 16-year-old female and a 22-year-old male each purportedly inhaled about ½ g of a white crystalline material purchased as "super-cocaine." According to the history given by the male, both became very intoxicated within 10 to 15 min after inhalation. The female became ill and went to the bathroom. The male subsequently passed out. When he regained consciousness, some 30 to 45 min later, he discovered the female unresponsive on the bathroom floor. She was pronounced dead on arrival at the hospital. The estimated time lapse between administration of the drug and arrival at the hospital was reported to be less than 2 h. The survivor complained of no adverse reaction when examined.

Pathology and Toxicology

The woman's lungs were edematous and hemorrhagic. Moderate cerebral edema and congestion of the kidneys were also noted.

Tissues and nasal swabs were taken at the autopsy, and a foil packet, which had contained the compound inhaled by the decedent and her companion, was obtained at the scene.

Residue from the foil was analyzed by thin-layer chromatography, ultraviolet and infrared spectrophotometry, and mass spectroscopy. Proparacaine was identified. The compound was also found present in nasal swabs from the decedent. The proparacaine used as a reference standard was supplied by Allergan Pharmaceuticals, Irvine, Calif. Samples of blood, brain, lung, and urine were screened for proparacaine by ultraviolet spectrophotometry and thin-layer chromatography. None was found.

A hydrolysis product of the parent drug was obtained by adding 2*N* HCl and boiling for 60 min (Fig. 1). The resulting hydrolysis product was found to extract as an amphoteric compound with an isoelectric point between pH 3 and 5. After adjusting the pH to this range, quantitative recovery was possible with multiple extractions of chloroform.

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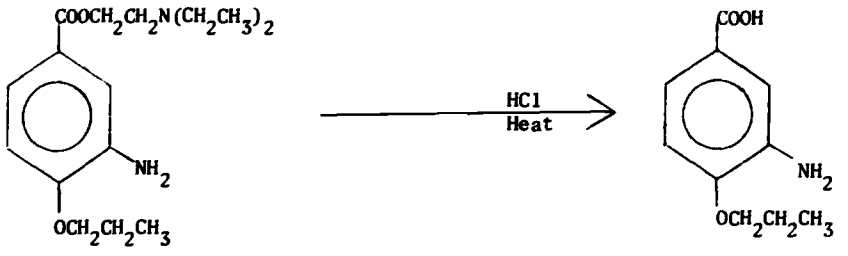

Proparacaine **Proparacaine Hydrolysis Product**

FIG. 1—*Hydrolysis reaction of proparacaine.*

Tungstic acid protein-free filtrates were prepared from blood, liver, kidney, and brain. Urine and gastric specimens were extracted without filtrate preparation.

With each of the specimens, the pH was adjusted to 4 and extracted five times with chloroform. The organic phase was extracted with 0.064*N* NaOH solution and scanned through the ultraviolet range of 340 to 220 nm. The solution was then made acidic with HCl and scanned again (Figs. 2 and 3). Quantitation was possible using either the absorbance at 295 nm in the base or 255 nm in the acid.

The aqueous phase was extracted back into chloroform and dried for further tests.

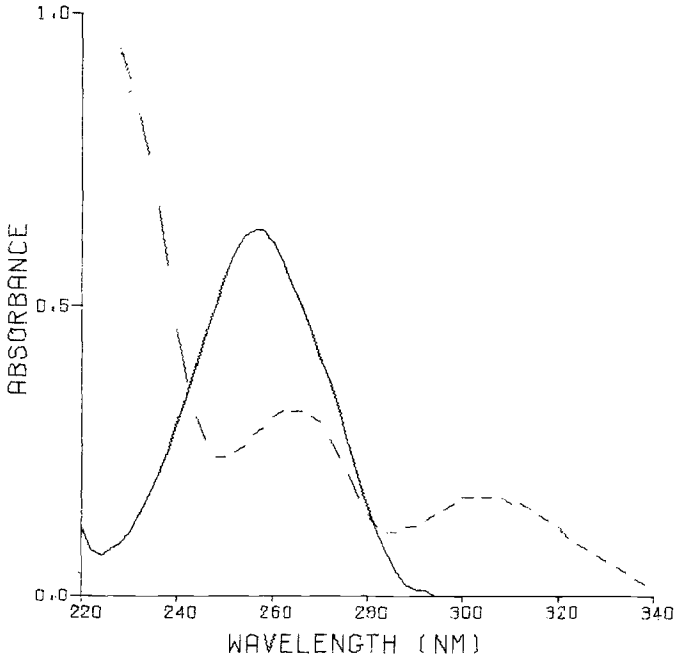

FIG. 2—*Ultraviolet spectra of proparacaine* (10 μg/ml). *The solid line represents the acid form of the drug and the broken line represents the basic form.*

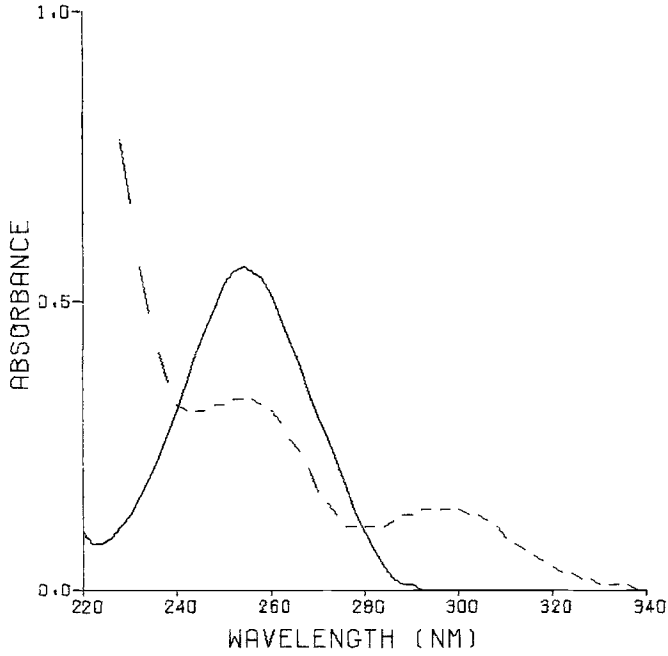

FIG. 3—*Ultraviolet spectra of proparacaine hydrolysis product (10 μg/ml). The solid line represents the acid form of the product and the broken line represents the basic form.*

Each residue was spotted on two silica gel thin-layer plates and developed in two separate solvent systems; System I, acetone:benzene:chloroform (20:40:40); and System II, benzene:chloroform:acetic acid (20:80:10). The position of the hydrolysis product, relative to caffeine, was 0.7 in System I and 1.6 in System II. The position of the parent compound was 1.8 relative to codeine in a methanol: ammonium hydroxide (200:3) solvent system using silica gel plates.

Ultraviolet spectra and thin-layer chromatographs of the tissue extracts were consistent with those of the hydrolysis product prepared from proparacaine. Tissue concentrations of the hydrolysis product are given as equivalent proparacaine in Table 1.

Blood, brain, liver, lung, and stomach were also screened for acidic, neutral, basic, and amphoteric drugs. None were found. Ethanol was found present in the blood in the concentration of 80 mg/100 ml.

TABLE 1—*Tissue concentration of hydrolysis product as equivalent proparacaine.*

Specimen	Amount, mg/100 ml or 100 g
Blood	1.5
Brain	0.4
Lung	1.2
Liver	1.7
Kidney	1.6
Urine	none detected
Stomach	none detected

Discussion

The pharmacology of proparacaine has been described by McIntyre and Sievers [*1*]. It has been shown to compare with tetracaine in potency [*2,3*]. Onset of action is rapid and anesthesia lasts about 15 min [*4*]. Little is known regarding the metabolism of the drug in man. According to a pharmacologist in a major firm which produces the compound, the nature of use of the drug is such that there has not been occasion to conduct metabolism studies in view of the minute amounts administered to man.[2]

Based on history, the lack of other significant causes of death, and toxicological findings, the cause of death in this case was determined to be "acute pulmonary and cerebral edema due to the inhalation of proparacaine."

Summary

A 16-year-old female died soon after inhaling proparacaine. Analysis of the tissues revealed an amphoteric compound consistent with a hydrolysis product prepared in the laboratory by reacting proparacaine with HCl in the presence of heat.

References

[*1*] McIntyre, A. R. and Sievers, R. F., "The Pharmacology of Some New Local Anesthetics," *Journal of Pharmacology and Experimental Therapeutics,* Vol. 63, 1938, pp. 369-390.

[*2*] McIntyre, A. R., Lee, L. W., Rasmussen, J. A., Kuppinger, J. C., and Sievers, R. F., "Laboratory and Clinical Trials of Five Local Anesthetics," *Nebraska State Medical Journal,* Vol. 35, No. 4, 1950, pp. 100-104.

[*3*] Goodman, L. S. and Gilman, A., Eds., *The Pharmacological Basis of Therapeutics*, 4th ed., MacMillan, New York, 1970, p. 385.

[*4*] Osol, A., Pratt, R., and Altschule, M. D., *The United States Dispensatory and Physicians' Pharmacology,* 26th ed., J. B. Lippincott Co., Philadelphia, 1967, p. 961.

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